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EXAMINER

SWITZER, JULIET CAROLINE

ART UNIT

PAPER NUMBER

1634

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/056,808

Applicant(s)

HINKEL ET AL

Examiner

Juliet C. Switzer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-17, 19, 20, 23 and 25-31 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 13-17, 19-20, 23, and 25-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_

### DETAILED ACTION

1. This action is written in response to applicant's paper received 6/9/04. Claims 13, 20, 23, 25, 28, and 30 were amended in this paper. Claims 1-12, 18, 21-22, 24, and 32-35 have been cancelled. Claims 13-17, 19-20, 23, and 25-31 are pending and examined herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL**

#### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 13, 14, 15, 16, 17, 20, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.* (Clinical Chemistry, 43(9):1749-1756 (1997)).

Lai *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

(a) providing at least one primer pair, said primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest and a hybridization tag that identifies the primer, said hybridization tag not complementary to the sequence containing said single nucleotide polymorphism of interest (§ 0179);

(b) combining said at least one primer with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (§ 0179);

(c) extending hybridized primers by primer extension to produce an extension product wherein said extension product comprises said hybridization tag and a detectable label (§ 0179);

(d) hybridizing said extension products by said hybridization tag or the complement thereof under stringent conditions to capture a probe wherein said capture probe is coupled to a microbead, said microbead identifying said capture probe (§ 0181, § 0182);

(e) detecting the hybridization of said extension product to said capture probe by the presence of said detectable label (§ 0182); and

(f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (§ 0182).

With regard to claim 14, Lai *et al.* teach that the reverse primer comprises a detectable label (§ 0179).

With regard to claim 15, Lai *et al.* further teach that the reverse primer is a universal primer that is universal to both alleles being tested (§ 0185, also figure 12).

With regard to claim 16, Lai *et al.* teach repeating the extension step in subsequent rounds of PCR (§ 0180).

With regard to claim 17, Lai *et al.* teach that this assay can be multiplexed, thus comprising a plurality of primer pairs specific for a plurality of single nucleotide polymorphisms (§ 0183).

With regard to claim 20, Lai *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one group of at least 2 primers in each group, wherein each primer comprises a hybridization tag that identifies said primer, and each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest (§ 0179 and § 0183);

b) combining said at least one group of primers with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (§ 0179, inherent in PCR);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (§ 0179-0180);

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d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a microbead that identifies said capture probe (§ 0182);

e) detecting the hybridization of said extension product to said capture probe using said detectable label (§ 0182);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (§ 0182).

With regard to claim 23, *Lai et al.* teach a method further comprising a plurality of said primer groups, each primer group specific for a different single nucleotide polymorphism of interest (§0183).

*Lai et al.* do not teach a method wherein the detection is by flow cytometry. (For clarity of the record, it is noted that *Lai et al.* at § 0264 do teach detection by flow cytometry. However, this disclosure is not supported by *Lai et al.*'s provisional application, which support is relied upon in this rejection).

*Fulton et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies (p. 1753-1755). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by *Lai et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by *Fulton et al.* One would have been motivated to utilize such methodology because *Fulton et al.* teach that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that

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their system "... is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy (p. 1775)." Thus, one would have been motivated to use flow cytometry to detect the microspheres taught by Lai *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

5. Claims 19, 25, 26, 27, 28, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.*, as applied to claims 13, 14, 15, 16, 17, 20, and 23 in the previous rejection, and further in view of Wallace *et al.* (WO 93/25563).

The teachings of Lai *et al.* in view of Fulton *et al.* are described in the previous rejection.

With regard to claim 19, Lai *et al.* in view of Fulton *et al.* do not teach the application of this methodology for diagnosing a disease, condition, disorder or predisposition. However, at the time the invention was made, it was routine in the prior art to utilize the detection of single nucleotide polymorphisms for the detection of any number of diseases. For example, Wallace *et al.* teach the detection of diseases such as sickle cell anemia or thalassemia caused by a defective allele (p. 5, first full paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the methods taught by Lai *et al.* in view of Fulton *et al.* for the detection of disease as suggested by Wallace *et al.* in order to have provided a method for detecting diseases caused by single nucleotide polymorphisms.

With regard to claim 25, Lai *et al.* in view of Fulton *et al.* do not teach methods wherein said primer extension is single base primer extension. Wallace *et al.* teach single primer extension for the detection of alleles, wherein the primer comprises a hybridization tag that identifies the primer (for example, p. 13-14). For example, Wallace *et al.* teach a hybridization based method for the detection of single nucleotide polymorphisms which comprises steps of

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hybridizing a group of at least two primers which comprise hybridization tags that identify the primers to sample, extending primers and hybridizing the extended primers to a capture probe (p. 9-10; p. 13-14; Figure 4 and 5). The method taught by Wallace *et al.* is a single base extension (see figure 4).

With regard to claim 26, the single base extension is achieved by using only a single type of nucleoside triphosphate, namely all deoxynucleotide triphosphates, and more specifically, to each extension reaction only a single labeled deoxynucleotide triphosphate was added (p. 13-14).

With regard to claims 27 and 28, Wallace *et al.* teach that the primer extension can be accomplished using chain terminating nucleotides, namely dideoxynucleoside triphosphates (p. 10, last line).

With regard to claim 31, Wallace *et al.* teach that their methods include methods for diagnosing diseases such as sickle cell anemia or thalassemia caused by a defective allele (p. 5, first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Lai *et al.* in view of Fulton *et al.* in order to have utilized the single nucleotide primer extension method taught by Wallace *et al.* One would have been motivated to utilize the methodology taught by Wallace *et al.* for allele specific detection because Wallace *et al.* specifically teach this as an application of their method and specifically suggest that the capture oligonucleotides of their method be attached to a solid support (p. 5). The combination of the methods of Lai *et al.* in view of Fulton *et al.* and further in view of Wallace *et al.* would have provided an alternative and effective method for the detection of polymorphisms in samples, useful, as taught by Wallace *et al.* for the detection of



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diseases such as sickle cell anemia. Therefore, in view of the teachings of Lai *et al.* in view of Fulton *et al.* and Wallace *et al.*, the instantly rejected claims are prima facie obvious.

6. Claims 13, 14, 15, 16, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace *et al.* (US5639611) in view of Gerry *et al.* (J. Molecular Biology, 292:251-262 (1999)) and further in view of Fulton *et al.*

With regard to claim 13, Wallace *et al.* (US) teach a method for detecting a single nucleotide polymorphism comprising:

(a) providing at least one primer pair, said primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest (Col. 2, lines 20-25; Col. 3, lines 50-57);

(b) combining said at least one primer with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (Col. 4, lines 1-5);

(c) extending hybridized primers by primer extension to produce an extension product wherein said extension product comprises said hybridization tag and a detectable label (Col. 4, lines 1-5);

Wallace *et al.* (US) further teach the capture of PCR products using a biotin-streptavidin interaction for the detection of a particular allele (Col. 3, lines 20-25).

With regard to claim 14, Wallace *et al.* (US) teach that either the forward or the reverse primer can contain a detectable label (Col. 6, lines 60-65).

With regard to claim 15, Wallace *et al.* (US) further teach that the reverse primer is a universal primer that is universal to both alleles being tested (Col. 3, lines 50-60, the BGP2 primer is used as the reverse primer for both alleles).

With regard to claim 16, Wallace *et al.* (US) teach repeating the extension step in multiple rounds of PCR (Col. 4, lines 5-10).

With regard to claim 19, Wallace *et al.* (US) exemplify the method for the detection of sickle cell anemia alleles, and specifically teach a method for diagnosing sickle cell anemia (Col. 3-4; Claim 3).

Wallace *et al.* (US) do not teach a method wherein the forward primer comprises a hybridization tag that identifies the primer, said hybridization tag not complementary to the sequence containing the single nucleotide polymorphism of interest, nor do they teach hybridizing extension products via the tag to a probe coupled to a particle, detecting the hybridization and identifying the single nucleotide polymorphism based upon the identity of said particle. Wallace *et al.* further do not teach a method wherein the at least one primer pair comprises a plurality of primer pairs specific for a plurality of single nucleotide polymorphisms.

Gerry *et al.* teach a universal DNA microarray method for multiplex detection of point mutations. In the methods taught by Gerry *et al.* allele specific primers are utilized which comprise a 3' end specific for an allele of a single nucleotide polymorphism of interest and a 5' that comprises a hybridization tag that identifies the primer, said hybridization tag no complementary to the sequence containing said single nucleotide polymorphism of interest (Figure 1(a); Table 3). After an allele specific reaction (in this case, ligase detection reaction), the reacted primers are hybridized to a capture probe and detected via a detectable label (p. 260,

second column). The location of the detection spot on the array (i.e. the identity of the particle to which the capture probe is coupled) identifies the polymorphism and allele present in the sample (p. 257, Figure 3).

With regard to claim 17, Gerry *et al.* teach a plurality of primers that are specific for a plurality of single nucleotide polymorphisms (p. 260).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Wallace *et al.* so as to have used the binary primer (having an allele specific portion and a hybridization tag) taught by Gerry *et al.* One would have been motivated to have modified the method taught by Wallace *et al.* in order to take advantage of the benefit of the “zip-code” arrays taught by Gerry *et al.*, who teach, “Since the zip-code sequences remain constant, and their complement can be appended to any set of LDR primers, our zip-code arrays are universal. Thus, a single array can be programmed to detect a wide range of genetic mutations... The universal zip-code array approach introduced here has the potential to allow rapid and reliable identification of low abundance mutations in multiple codons of numerous genes (p. 258-259).” Thus, the use of the zip-code methodologies taught by Gerry *et al.* with the methods of Wallace *et al.* would have afforded one of ordinary skill in the art the opportunity to expand the methods taught by Wallace *et al.* for the detection of multiple mutations and codons.

The teachings of Wallace *et al.* in view of Gerry *et al.* do not teach a method wherein the capture probes are attached to microbeads and wherein the detection occurs by flow cytometry.

Fulton *et al.* teach a method which is very similar to the method taught by Wallace *et al.* in view of Gerry *et al.* in that it utilizes primers with capture tags which are used to differentiate

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primers in a sample via hybridization to a tag complement. Fulton *et al.* utilize capture probes attached to microbeads and detection via flow cytometry. Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies (p. 1753-1755). Fulton *et al.* teach the multiplexed assays which utilize the microspheres are suitable for use with oligonucleotide target molecule (p. 1750), and teach that with respect to hybridization assays that the no-wash format of many microsphere-based assays, particularly in the final detection step, is considerably faster than assays that require multiple washings (p. 1755). They also teach that the rapid kinetics of microsphere-based assays that allow shorter incubation times than conventional solid supports (p. 1755).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Wallace *et al.* in view of Gerry *et al.* so as to have provided a microsphere based assay that included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.* One would have been motivated to utilize such methodology because Fulton *et al.* teach that their system “represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions...” and that their system “...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis...” offering “excellent sensitivity, precision, speed, and economy (p. 1775).” Thus, one would have been motivated to use flow cytometry to detect the microspheres taught by Wallace *et al.* in view of Gerry *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

7. Claims 20, 23, 25, 26, 27, 28, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* in view of Dubiley *et al.* (Nucleic Acids Research, 1999, Vol. 23, No. 18, page e19).

With regard to claim 20, Chen *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one oligonucleotide primer comprising a hybridization tag that identifies said primer, said primer having a 3' end specific for a single nucleotide polymorphism of interest (p. 550, Col. 1, the primer has a DNA sequence at the 5' end that allows the primer to be captured onto a microbead);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (p. 556, "SBCE reactions," Figure 1);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (p. 556, "SBCE reactions," Figure 1);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (p. 556, "Hybridization of SBCE Reaction Mixture to Microsphere");

e) detecting the hybridization of said extension product to said capture probe using said detectable label (p. 556);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (p. 557).

With regard to claim 23, Chen *et al.* teach that the present invention can be used for the determination of which alleles are present at 4 different SNP (p. 550, Figure 2), and such a method would inherently include the use of a plurality of primers each specific for a different single nucleotide polymorphism.

Chen *et al.* teach a method wherein the 3' end of said primer is immediately adjacent to the location of the single nucleotide polymorphism of interest (p. 556).

With regard to claim 25, the method taught by Chen *et al.* is a single base extension (i.e. the method is called "Single Base Chain Extension" throughout.).

With regard to claim 26, the single base extension is achieved by using only a single type of nucleotide triphosphate, namely all dideoxynucleotide triphosphates (p. 556, SBCE Reactions).

With regard to claims 27 and 28, Chen *et al.* exemplify primer extension can be accomplished using chain terminating nucleotides, namely dideoxynucleoside triphosphates (p. 556, SBCE Reactions).

Chen *et al.* do not teach a method wherein said at least one primer comprises a group of at least 2 primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest. With regard to claim 31, Chen *et al.* do not teach or suggest the application of these methodologies to the detection of disease or conditions.

Dubiley *et al.* teach a single nucleotide extension method for the detection of polymorphic alleles which utilized primers that contain different 3'-terminal nucleotide

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overlapping the variable DNA, and teach a group of at least 2 primers, each primer having a 3' end specific for different alleles of a single nucleotide polymorphism of interest (heading: Materials and Methods; Isothermal single base primer extension assay; Identification of a single base polymorphism with multiprimer assay). In the multiprimer assay, four primers variable at the 3' nucleotide are used to test all four possible bases in the polymorphic site of target DNA (heading: RESULTS; Amplified multibase and multiprimer single-stranded extension). Furthermore, Dubiley *et al.* teach the application of single base extension methodologies to  $\beta$ -Thalassemia diagnosis (heading: RESULTS;  $\beta$ -Thalassemia diagnostics).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have utilized the primers taught by Dubiley *et al.* in the methods taught by Chen *et al.* so as to have provided a method which utilizes a pair of at least two primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest, and further to have utilized the polymorphism detection methods for the detection of disease related alleles. The use of such primers would have provided an alternate methodology for the detection of single nucleotide polymorphisms using the basic methodology taught by Chen *et al.*, as Dubiley *et al.* teach that the use of primers that end adjacent to or overlap with the polymorphic site have comparable specificity with regard to one another (final page, first full paragraph). The use of the method for the detection of disease alleles would provide the obvious benefit of detecting disease alleles and thus the presence or predisposition to disease.

8. Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* in view of Dubiley *et al.* as applied to claims 20, 23, 25, 26, 27, 28, and 31 above, and further in view of Söderlund *et al.* (US 6013431).

The teachings of Chen *et al.* in view of Dubiley *et al.* are applied to claims 29 and 30 as they are applied in the rejection of claims 20, 23, 25, 26, 27, 28, and 31.

While Chen *et al.* utilize labeled chain terminating nucleoside triphosphates, namely dideoxynucleoside triphosphates, Chen *et al.* do not teach a method wherein a plurality of chain-terminating nucleoside triphosphates (p. 555), each comprising a unique label are used, as is recited in claims 29 and 30.

Söderlund *et al.* teach single nucleotide primer extension methods which a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used for the detection of more than one point mutation occurring at the same site out of one undivided sample (Col. 8, lines 44-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Chen *et al.* so as to have included differentially labeled ddNTPs as taught by Söderlund *et al.* within the reaction mixture in order to detect more than one point mutation occurring at the same site of an undivided sample.

9. Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.* and Wallace *et al.* (WO93), and further in view of Söderlund *et al.*

The teachings of Lai *et al.* in view of Fulton *et al.* and Wallace *et al.* are applied to claims 29 and 30 as they were previously applied to claims 19, 25, 26, 27, 28, and 31.



While Wallace *et al.* teach methods which utilize labeled chain terminating nucleoside triphosphates, namely dideoxynucleoside triphosphates (p. 10, last line), Wallace *et al.* do not teach a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used, as is recited in claims 29 and 30.

Söderlund *et al.* teach single nucleotide primer extension methods which a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used for the detection of more than one point mutation occurring at the same site out of one undivided sample (Col. 8, lines 44-48).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Lai *et al.* in view of Fulton *et al.* and Wallace *et al.* so as to have included differentially labeled ddNTPs as taught by Söderlund *et al.* within the reaction mixture in order to detect more than one point mutation occurring at the same site of an undivided sample.

10. Claims 20, 23, 25, 26, 27, 28, 29, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al.* in view of Fulton *et al.*

With regard to claim 20, Huang *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one a group of at least 2 primers in each group, wherein each primer comprises a hybridization tag that identifies said primer, and each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest (Col. 2, lines 50-55; Col. 4, lines 20-25; Col. 17, lines 55-60; Claim 15);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (Col. 2, lines 45-50);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (Col. 2, lines 55-57);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (Col. 2, lines 57-59);

e) detecting the hybridization of said extension product to said capture probe using said detectable label (Col. 4, lines 14-16);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (Col. 5, lines 43-52).

Huang *et al.* teach that this assay can be multiplexed, thus comprising a plurality of primers specific for a plurality of single nucleotide polymorphisms (Col. 4, lines 20-25). Huang *et al.* teach a method wherein said at least one primer comprises a group of at least 2 primers, each primer specific for a different allele of a single nucleotide polymorphism of interest (Col. 17, lines 55-60; Claim 15).

With regard to claim 23, Huang *et al.* teach a method further comprising a plurality of said primer groups, each primer group specific for a different single nucleotide polymorphism of interest (Col. 4, lines 20-25).

With regard to claim 25, Huang *et al.* teach a method wherein said primer extension is a single base primer extension (Col. 8, line 58).

With regard to claim 26, Huang *et al.* teach a method wherein said single base extension is achieved by using only a single type of nucleoside triphosphate, that is dideoxynucleotide triphosphates (Col. 8, line 59).

With regard to claims 27, 28, and 30, Huang *et al.* teach a method wherein said single base extension is achieved by using at least one chain terminating nucleotide triphosphate (Col. 8, line 59).

With regard to claim 29, Huang *et al.* teach that two different fluorescent labels can be used in order to distinguish between two alleles at each polymorphic site examined (Col. 17, lines 55-56).

With regard to claim 31, Huang *et al.* teach that their methods can be employed to detect mutations and identify phenotypes of mutations in clinical diagnostics and clinical studies (Col. 7, lines 25-30).

Huang *et al.* teach that the solid support can be beads (Col. 5, line 46, and claim 7).

Huang *et al.* do not teach a method wherein the detection is by flow cytometry

Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies (p. 1753-1755). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Huang *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.* One would have been motivated to utilize such

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methodology because Fulton *et al.* teach that their system “represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions...” and that their system “...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis...” offering “excellent sensitivity, precision, speed, and economy (p. 1775).” Thus, one would have been motivated to use flow cytometry to detect the microspheres taught by Huang *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

#### **Response to Remarks**

New grounds of rejection are set forth to address the amended claims.

The rejection of claims 20, 21, 24, 25, 26, 27, 28, and 31 under 35 U.S.C. 102(b) as being anticipated by Wallace *et al.* (WO 93/25563) is WITHDRAWN in view of the amendments to the claims and the arguments presented at least on page 10 of the response.

The rejection of claims 20, 21, 24, 25, 26, 27 and 28 under 35 U.S.C. 102(a) as being anticipated by Chen *et al.* (Genome Research, April 2000, 10:549-557) is withdrawn in view of the amendments to the claims and in view of the arguments of record found at p. 12 of the response (3<sup>rd</sup> ¶).

The rejection of claims 13, 14, 15, 16, 17, 20, 21, 22, and 23 under 35 U.S.C. 102(e) as being anticipated by Lai *et al.* (US 2003/0049620, filing date, 4/30/01, provisional filed 4/28/00) are withdrawn in view of the amendments to the claims and the arguments on at least page 16 of the response.

The rejection of claims 20, 21, 22, and 23 under 35 U.S.C. 102(e) as being anticipated by Huang *et al.* (US 6287778 B1) is WITHDRAWN in view of applicant's amendments to the claims, as discussed on p. 21 of the response.

The rejection of claim 13-17 and 19 under Wallace *et al.* (US) in view of Gerry *et al.* has been withdrawn in view of the amendments to the claims. A new grounds of rejection under Wallace *et al.* (US) in view of Gerry *et al.* and further in view of Fulton *et al.* has been set forth to address the amendments to the claims.

The application of Lai *et al.* in view of Fulton *et al.* to claim 18 is moot in view of the cancellation of claim 18. However this rejection is newly applied to amended claims 13, 14, 15, 16, 17, 20, and 23. The arguments regarding this rejection are addressed insofar as they apply to the pending rejection.

Applicant argues at page 28 that the rejection is improper "in that the suggestion or motivation to combine the references is not supported by the proposed combination of references...and there is no reasonable expectation of success of a method derived from the combined teachings." These arguments are not persuasive.

Regarding the motivation, as discussed in the rejection, Fulton *et al.* specifically teach that the use of microbeads and flow cytometry detection have a wide range of applications. To that end, at page 1750 of the reference, second column, Fulton *et al.* give guidance as to how to apply the use of microbeads to a wide variety of target molecules, including oligonucleotides. At p. 1755, Fulton further expand their discussion of the benefits and wide applicability of their system teaching that "the system has several advantages for analysis of biologically and medically relevant molecules, including speed, economy, and advanced analytical

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capabilities..." and further specifically suggest the use of the system for capture/sandwich assays, which is precisely the type of system that Lai *et al.* are using. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation has been cited in the rejection, and this specific motivation is found in the teachings of Fulton *et al.*

At page 29 of the response, application states that "one of skill would have to engage in considerable experimentation in order to reconcile the two teachings" and that there is no reasonable expectation of success if the two teachings were combined. However, these are attorney's arguments which are not supported by any evidence on the record, and which Fulton *et al.*'s teachings of the broad applicability of their method seem to contradict. As previously discussed, Fulton *et al.* are very clear in their suggestion that their methods using microspheres and flow cytometry have wide applicability to a variety of different binding assays, specifically mentioning oligonucleotide binding and capture assays. Absolute predictability is not required in order to establish an expectation of success. The MPEP states, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness (2143.02)." However, in the instant case, no evidence is presented, only the arguments of counsel. The arguments of counsel are not found to be persuasive in the absence of a factual showing. MPEP 716.01(c) makes clear that

"The arguments of counsel cannot take the place of evidence in the record. In *re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

On page 30 of the response, applicants compare the hybridization and capture method exemplified in *Fulton et al.* with that of *Lai et al.* In the instant rejection, *Lai et al.* provides all of the method steps of the claimed invention except the use of flow cytometry. The suggestion to combine the references is a suggestion to modify the method taught by *Lai et al.* so as to take advantage of the "revolutionary" methods taught by *Fulton et al.* Applicant's arguments focused on an exemplified embodiment of *Fulton et al.*, but do not consider the totality of the reference and the specific teachings of *Fulton et al.* as to the wide applicability of their method. MPEP 2123 teaches that "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments." In the instant case, *Fulton et al.* exemplify the use of the microbeads with a competition hybridization assay, but suggest its wide applicability to any analyte binding assay, specifically mentioning sandwich and capture assays.

Applicant argues at page 31 that the examiner has used improper hindsight reasoning to combine the two prior art references. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge

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gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the combination of references flows directly out of the prior art, with the teachings of Fulton *et al.* specifically suggesting the application of their methodology to a wide variety of multiplex assays and the teachings of Lai *et al.* providing an assay that is carried out on microbeads which would be an obvious choice for modification for use with the teachings of Fulton *et al.* The rejection is MAINTAINED.

The rejection under Lai *et al.* in view of Wallace *et al.* was withdrawn in view of the amendments to the claims, as clearly discussed in applicant's arguments at pages 32-33 of the response.

The application of Wallace *et al.* in view of Gerry *et al.* and further in view of Fulton *et al.* to claim 18 is moot in view of the cancellation of claim 18. However this rejection is newly applied to amended claims 13, 14, 15, 16, 17, and 19. The arguments regarding this rejection are addressed insofar as they apply to the pending rejection.

Applicant argues at page 36 that the rejection is improper "in that the suggestion or motivation to combine the references is not supported by the proposed combination of references...and there is no reasonable expectation of success of a method derived from the combined teachings." These arguments are not persuasive.

Applicant's consideration on page 38 of each of the methods of Wallace *et al.*, Gerry *et al.*, and Fulton *et al.* do not consider the totality of the rejection but instead consider only the specifically disclosed embodiments of the references, particularly with regard to the teachings of Fulton *et al.* This type of argument has been thoroughly addressed with regard to the rejection of



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Lai *et al.* in view of Fulton *et al.*, and those arguments apply in this case as well. Namely, Fulton *et al.* clearly suggest broad applicability of their method to many types of binding assays, in particular mentioning capture assays and hybridization assays. The reference must be considered for the totality of its teachings. Further, applicant has not provided any evidence of record to support the argument that there is no reasonable expectation of success. As such, the rejection is applied to the amended claims.

The application of Chen *et al.* in view of Dubiley *et al.* to claim 22 is moot in view of the cancellation of claim 22. However this rejection is newly applied to amended claims 20, 23, 25, 26, 27, 28, and 31. The arguments regarding this rejection are addressed insofar as they apply to the pending rejection.

Applicant argues at page 41 (2<sup>nd</sup> ¶) that there is no motivation to combine the references, and that the references discourage such a combination. In support of this argument, applicants discuss the differences in methodology between Chen *et al.* and Dubiley *et al.* suggesting that the methods are not combinable. However, this is not persuasive. Dubiley *et al.* are relied upon to provide teaching of a particular type of sets of primers; Chen *et al.* provide all of the other elements of the claims. Applicant's analysis of the two methods does not take in consideration the totality of the rejection which describes the necessary modification to Chen *et al.* or the motivation given to modify the method taught by Chen *et al.* in order to have arrived at the claimed invention. Applicant states that Chen *et al.* would not have been motivated to utilize the solid phase assays taught by Dubiley *et al.* as the methods of Chen *et al.* were more amenable to multiplexing. The examiner has not argued that one would be motivated to use the solid phase assay of Dubiley *et al.*, but instead to have modified the primers taught by Chen *et al.* so as to

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have used those taught by Dubiley *et al.*, and such a modification would have been motivated in order to provide an alternate methodology for the detection of single nucleotide polymorphisms using the basic methodology taught by Chen *et al.*, as Dubiley *et al.* teach that the use of primers that end adjacent to or overlap with the polymorphic site have comparable specificity with regard to one another (final page, first full paragraph). The use of the method for the detection of disease alleles would provide the obvious benefit of detecting disease alleles and thus the presence or predisposition to disease. Therefore, the rejection is applied to the amended claims.

The rejection under Chen *et al.* in view of Soderlund *et al.* is withdrawn in view of applicant's amendments to the claims as discussed in the response at pages 44-45.

The rejection under Wallace *et al.* in view of Soderlund *et al.* is withdrawn in view of applicant's amendments to the claims as discussed in the response at pages 46-47.

The claim objections are withdrawn in view of the amendments.

New grounds of rejection are set forth to address the amendments to the claims.

### ***Conclusion***

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

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CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

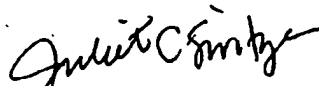
The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Juliet C. Switzer  
Examiner  
Art Unit 1634

September 6, 2004